



Evaluation of Carbon Dioxide Angiography in Management of Critical Lower Limb Ischemia with Infrapopliteal Arterial Disease

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Abstract

The aim of the study is to elaborate on the understanding of the application of the CO₂ angiography in obtaining quality imaging of infrapopliteal diseased arteries by digital subtraction CO₂ angiography, and angioplasty using the automated Angiodroid CO₂ injector® (primary outcome). This is a retrospective observational non-randomized study that included 23 patients of critical LL ischemia having infrapopliteal disease alone or combined with the femoropopliteal disease along with typical renal impairment. Carbon dioxide digital subtraction angiography (CO₂ DSA) was used for all the patients and the outcomes were subjected to the comparison by iodinated contrast by an operator. The study included 17 female and 6 male subjects. The age group of the patient was between 48 years and 78 years. The mean age was 61.8 ± 11.1 years. The quality of the images obtained from the CO₂ DSA method adopted was categorized as: good images (9) 39%, Accepted (8) 34%, and bad (6) 26% images. No complication from CO₂ injection occurred for the patients, while leg pain was recorded in 4 patients during the CO₂ injection (17.3%). The trial outcome elaborated and supported the safety of using CO₂ angiography in the diagnosis and management of critical LL ischemia with infrapopliteal disease.

Keywords: Carbon Dioxide; Angiography; Critical Limb; Ischemia

Abbreviations: PAD: Peripheral Arterial Disease; CLI: Critical Limb Ischemia; DSA: Digital Subtraction Angiography; CDA: Carbon Dioxide Angiography; IC: Iodinated contrast; CIN: Contrast-Induced Nephropathy

Introduction

Peripheral arterial disease (PAD) or Peripheral vascular disease is predominant in the global population presently. Recent analysis suggests that more than 200 million people are having PAD [1]. Specific diagnosis of PAD especially the infrapopliteal disease remains the key for management [2]. Endovascular therapy with iodinated contrast is considered the main stay but sometimes it is not suitable for renal impairment patients [3]. Carbon dioxide angiography is considered then as an alternative contrast for endovascular diagnosis and management of critical limb ischemia especially

those who are diabetics and have renal impairment [4,5]. The incidence of contrast induced nephropathy in peripheral arterial disease patient is 3% [6]. Prevention of this problem included decreasing the amount of contrast used, also CO₂ as a contrast can be used as it is neither nephrotoxic nor allergic [7,8]. The use of carbon dioxide is useful however the quality of image is doubtful [9].

Methods

Patient Selection

This is a retrospective observational non-randomized study that included 23 patients having Critical Limb Ischemia (CLI). All the selected patients were having renal impairment either accompanied with infrapopliteal disease alone or in combination with the femoropopliteal disease.

The recruitment of the patients was done at the Outpatient Clinic of the Vascular Surgery Unit in Kasr alainy University Hospital. The patient recruitment was conducted for two years (June 2017-May 2019). We confirm the approval of the Medical Committee of Vascular Surgery Department that this work is ethically accepted and all patients have signed and approved to be in the study.

Inclusion and Exclusion Criteria

The inclusion criteria of the patients included Critical LL ischemia with only infrapopliteal disease or infrapopliteal disease along with femoropopliteal disease clinically established. The presence of Diabetic nephropathy was another important inclusion criteria decided for this study. Similarly, patients having certain characteristics were excluded from the study such as patients who were having end-stage renal disease and the patients having a normal renal function and were not diabetic.

Pre-procedure data recording

All the selected patients were investigated strictly considering the inclusion and exclusion criteria mentioned and records on the clinical and medical history, outcome of the clinical examination and routine laboratory investigations were collected systematically. Additionally, information on their duplex scan of both the lower limbs from the Aorto-iliac position to both the pedals was carefully investigated and recorded.

Procedure Preparation

All patients were done in the Angiosuite. In this process, Carbon Dioxide Angiography (CDA) was used to fulfill the purpose.

Angiosuite Set Up

The angiography was done by Philips AlluraXper® FD 20/722028164 system that is compatible with the automated Angiodroid CO₂ injector® that had important required features such as digital subtraction angiography (DSA), CO₂ software, frame rate at least 4-6 fps, road mapping, CO₂ stacking, contrast enhancement, pixel shift, and inversion scale. Iodinated contrast (IC) was used with variable amounts to confirm and compare the CO₂ DSA.

Pre-Procedure Preparation

In this process, clopidogrel 75 mg (4 tablets = 300 mg) was used as the loading dose, intravenous hydration (0.5-1 ml/kg/hr., normal saline) was applied and continued after the procedure for 12 hours. The individual patient was

instructed to lie in the supine position with a 30-degree inclination in a Trendelenburg position as a safety measure. The patients were having proper immobilization for accurate x-ray and were also having compatible external bandage.

Procedure

During the procedure, local anesthesia was used at the puncture site when ipsilateral common femoral artery access was done with 6FG and 10 ml of CO₂ was injected to replace the air in the tubes and to prevent the formation of the air bubbles. The volume of CO₂ injection (10-100 ml) applied per injection was dependent on the target site and the catheter size. In the present study, the volume injected was 30 ml for infrapopliteal angiography (selective 5 FG catheter 60 cm long), and 20 ml was injected through femoral sheath when the patient was undergoing popliteal angiography. While using a short catheter, the pressure setup was 200 (150-250) mm Hg, and 400 (350-450) mm Hg was set when micro catheters or long introducers were used. Usually, the pressure was set to 30 mmHg above the patient's systolic blood pressure in case of the use of short catheters. Interval of 1-2 min was allowed between the repeated CDA procedures. For each case, CO₂ stacking, contrast enhancement, pixel shift after processing, and inversion scaling were done carefully. To have high-resolution images, CO₂ DSA was conducted for the infra-popliteal area. Unlike conventional DSA with IC, immediate evaluation of the images was avoided as many images (6 frames/sec) were integrated [9]. Analyses were done frame by frame along with capturing the better images through using the subtraction button [10]. This setup allowed better visualization of infrapopliteal angiography images as well as caused reduced pain to the patient. During this process, the amount of CO₂ injected, the pressure of CO₂ used, and the amount of iodine confirmatory contrast obtained was recorded. The quality of the imaging obtained by the CO₂ distal subtraction angiography was compared with the iodine contrast digital subtraction angiography by an operator using the subjective method.

Quality analysis of CO₂ DSA Angiography

The images obtained from CO₂ DSA were compared with the iodinated contrast iopromide by an independent operator using (Ultra vist®) at 12 points where each tibial had 4 zones. Each zone was scored as "1" if found good, or "0" if found not acceptable. Later, the sum was calculated. The 4 zones considered were:

- I: From just above the malleoli till the foot
- II: Above malleoli for the distal 1/3 of the leg
- III: Second (2nd) 1/3 of the leg
- IV: Proximal first 1/3 of the leg from below neck of the fibula.

The obtained quality of the CO₂ DSA imaging was further

divided into 3 categories (Good, accepted, bad) according to the Philips proprietary post-processing software as defined in the following section.

- **Good:** Adequate image quality for appropriate diagnosis that can allow proceeding with the intervention [10-12].
- **Accepted:** Adequate image quality for diagnosis, but needed confirmatory Iodinated Contrast (IC) to proceed with the intervention [7-9].
- **Bad:** Inadequate image quality for proper diagnosis and intervention. (IC) must be used for these imaging (6 and below 6).

Data availability

The authors confirm that the data supporting the findings of this study are available within the article.

Results

Population, comorbidities, CLI

Twenty three (23) patients were considered in this study with CLI infrapopliteal disease & renal impairment. These patients underwent angioplasty using CO₂ as a contrast. The study included 17 females and 6 males. The observed age group was 48-78 years. The mean age observed was 61.8 ± 11.1 years.

The risk factors associated with considered patients were: Diabetes mellitus (n=21) 91%, Hypertension (n=21) 91%, Ischemic Heart Disease (n=9) 39%, Renal complications (n=19) 82% and Cerebrovascular stroke (n=5) 21%.

The Rutherford classification of the critical limb ischemia was as following: Class V: n=16 (70%), Class VI: n=7 (30%). The distribution of the lesions recorded was as following: the superficial femoral artery (SFA) with infrapopliteal disease was in 17 (73.9%) patients, and Infrapopliteal disease alone was present in 6 (26.1%) patients.

Imaging Quality Analysis

CO₂ angiography was used in 21 cases and 2 cases were exempted due to allergy to the iodine. The mean pressure for injection was 170 ± 18 mm Hg, and the mean total volume for each case was 220 ± 48 ml. No complication from CO₂ injection occurred in these patients, while leg pain was recorded in 4 cases during CO₂ injection (17.3%). During the process, we observed that the diagnostic value of CO₂ angiography in the infrapopliteal arteries was least consistent in the distal segments due to the motion artefact caused by leg pain during injection. However, selective catheterization, leg elevation, patient cooperation, analgesia, and local administration of vasodilators, may be helpful (Figures 1-3).



Figure 1: (A) Representation of the CO₂ DSA of popliteal and infrapopliteal arteries. (B) IC DSA representation of the same image of popliteal and infrapopliteal regions.

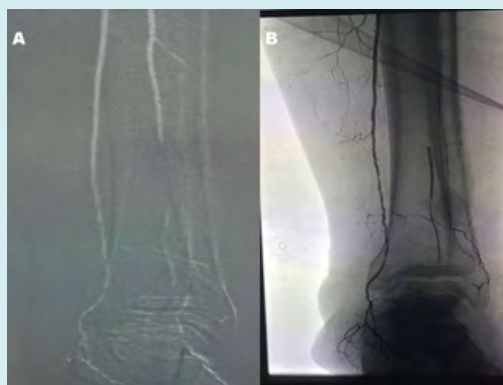


Figure 2: (A) CO₂ DSA patent posterior tibial artery, occluded middle 1/3 of the peroneal artery, non-visualized anterior tibial artery. (B) IC DSA presentation of the patient's posterior tibial artery occluded middle 1/3 of the peroneal artery, and non-visualized anterior tibial artery.

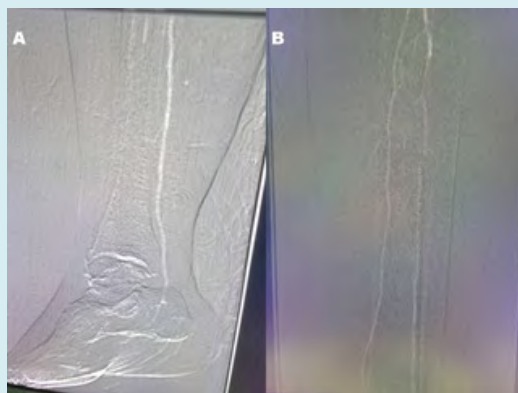


Figure 3: (A) CO₂ DSA showing the posterior tibial artery as the only runoff. (B) CO₂ DSA showing properly visualized posterior tibial and peroneal artery.

Renal Function Follow-Up

Contrast-Induced Nephropathy (CIN) is considered by >25% increase or > 0.5 mg/dL (44.2 μ mol/L) in serum creatinine level within the 3 days of intravascular contrast administration. However, the absence of an alternative cause remains another major criterion. The amount of confirmatory diluted iodinated contrast ranged from 0-35 ml with an average of 15.77 ml. Therefore, the actual amount was 7.88 ml. The purpose and application of IC were presented as confirmatory (n=17), ineffective (n=6), and not used (n=2) for the patients in this study. There were a total of 3 cases of Contrast-Induced nephropathy (CIN), one patient was having dialysis and died after 1 month due to septic shock after BKA. The others recovered to their baseline creatinine level as recorded during the preoperative stage. There were 2 cases of mortality in the whole study (8.6%).

Pain Perception during CO₂ Angiography

A total of 4 patients experienced various degrees of transit pain (mild to moderate) (1-6 in scale of 10) during automated CO₂ injection for angiography and angioplasty. No additional pain killers were required.

Discussion

Proper diagnosis and accurate invasive procedure determine the success rate of angioplasty, especially, for the patients having severe complications such as CLI. CO₂ as contrast has been used for a long time in endovascular therapy [4]. Specifically, in patients who have renal impairment, such procedures become essential, however, often such patients are expected to have Contrast-Induced nephropathy (CIN) or known to have some kind of contrast-induced allergy [8]. Technically, for better imaging and diagnosis requirement, endovascular therapy requires the use of iodinated contrast. However, this increases the incidence of Contrast-Induced nephropathy (CIN), especially in the diabetic patient [11,12].

The use of CO₂ as a contrast medium is still noisy to the physicians, especially, if the target vessels are infrapopliteal arteries which require higher precision and accuracy for diagnosis and treatment. Motion or artifact derived comparatively poor quality of images derived from CDA remains a major challenge in this issue. The experience and expertise of the radiologist play a pivotal role in interpreting the images in such circumstances. In the present study, such a problem was countered by using 6 frames/sec imaging with better subtraction, pixel shifting, and image stacking.

The use of high-quality imaging machine with high resolution of more the 1024 X 1024 pixels analyzed with the sophisticated software in the imaging machine, allowed us to

have high-quality CO₂ imaging. Further, due to the integration of multiple images and frame-wise analysis, the outcomes of the observations were accurate. A similar report is done by Cho as well [9]. The state-of-the-art machinery used in this analysis also supported tremendously in the reduction of the artifacts and false-positive outcomes. Another important technical problem of air contamination was managed by using the air filter and injecting 10 ml of CO₂ in this study. The other issue is the pain triggered during the CDA process due to the gas explosion caused by compressed gas was managed through clearing the catheter and system by flushing them with 10 ml of CO₂. However, the existing literature suggested the application of only 3-5 ml of CO₂ to flush the catheter [9]. Moreover, the automated process injected in small volumes for the automatically targeted preset pressure yielded better imaging quality and lesser pain to the patient.

The volume used was only 20 ml of CO₂ with 30 mmHg pressure exceeding the systolic pressure of the patients. Therefore, customization was done for each of the patients for a better outcome. The followed intervals of 2 min also supported the outcomes. Besides, the imaging of the infrapopliteal arteries using a catheter placed in the lower popliteal allowed better visualization of infrapopliteal arteries and also provided better visualization of the whole popliteal artery due to the reflux criteria. Such criteria were not present in other iodinated contrast as mentioned by Giordano, et al. [10] Other reports suggested the use of the old mechanical injector that remained comparatively complicated to handle and were having an effect on the outcome as well [13]. However, we have adopted the selective angiography process similar to the study by Cheng-Feng, et al. unlike the external bandage, patient alignment at the 30 degrees Trendelenburg position. Interestingly, in their experiments 3 patients were unable to complete the procedure due to the intense leg pain, however, they have mentioned that reduction of the CO₂ volume from 80-100 ml to 40-60 ml yielded some benefits and relief in the leg pains of the patients. Similarly, we have also used a reduced volume that helped us made the pain of the patients bearable. Another study conducted by Fujihara, et al. excluded the patient having infrapopliteal disease, but the study reported the benefit of using the CO₂ angiography in infrainguinal disease [8]. Our outcomes were comparatively better with such complicated angioplasty. However, the present study is having certain limitations. The study is a single armed registry and was conducted on only a small number of patients who are known to have an allergy to iodinated contrast or who have renal impairment of Rutherford V and VI-grade. Also, the evaluation of images was done by a single operator; hence, manual expertise was considered. On the contrary, the present study followed almost a standard process for all the patients, thus, ensuring the high quality of the angiographic images and the diagnosis outcomes.

Conclusion

The trial elaborated on the safety of using CO₂ angiography in the diagnosis and management of CLI with infrapopliteal disease which remains a challenge in medicine even now. The procedure causes some leg pain and requires caution in the adjustment of the administered CO₂ volume and pressure. In the future, with the precise tuning of the volume and pressure, the outcome may become much favorable to the patient and the radiologist. Moreover, the CO₂ may replace other iodinated contrast as it is cheaper than the iodinated contrast. Good quality images, nontoxic property, the repetitive possibility of application, absence of renal complication, higher solubility, injection through small diameter catheters, can make this process a game-changer in this specific type of diagnosis and procedure. More future experiments can also allow standardizing the application of CO₂ angiography and helping in numerous patient CLI treatment, management, and recovery.

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